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# *Urinary Tract Infections*

ERNEST JAWETZ

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## Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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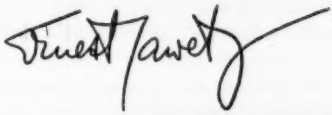

received his Ph.D. in medical microbiology in 1942 while engaged in war-time research on plague at the Hooper Foundation for Medical Research, the University of California. In 1946 he was awarded his M.D. from Stanford University and served as house officer in internal medicine at Stanford-Lane Hospital during the early years of the "antibiotic era." From this period stemmed his interest in antimicrobial chemotherapy. Subsequently he spent two years in clinical and laboratory research at the National Institutes of Health, and since 1948 has been on the faculty of the University of California School of Medicine, where he is Professor of Microbiology and Lecturer in Medicine and Pediatrics. The investigations of his group on antibiotic synergism and antagonism have attracted wide attention, and he had presented them in this country in many medical centers as well as abroad (Almroth Wright Lecture 1952, St. Mary's Hospital Medical School, London; MacArthur Lecture 1952, University of Edinburgh).

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INFECTIONS OF the urinary tract are probably second in frequency only to those of the upper respiratory tract. In the urinary tract the infectious process deserves attention not only for its own sake, i.e., because of the symptoms and signs it produces, but also because it often results in progressive and irreversible impairment of kidney function. There are available a number of good and detailed discussions dealing with specialized phases of the urological and medical management of urinary tract infections. This review adds no important new facts or startling developments. Rather, it attempts to reassess the changing problems of the management of urinary tract infection from the standpoint of pathogenesis and natural history of the disease. It is the author's belief that the development of a comprehensive point of

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view is far more important than a listing of the "latest" in drugs and treatment methods—which must, of necessity, be out of date by the time a review appears in print. An attempt will therefore be made to stress principles of diagnosis and management without detailed "cookbook" recipes for treatment, which would only insult the reader's intelligence.

DEFINITIONS.—Infections of the urinary tract have often been classified according to their anatomic location into urethritis, prostatitis, cystitis, ureteritis, pyelitis and pyelonephritis. Some of these terms have continuing utility in describing the location of the most marked inflammatory response within the tract, but in the vast majority of patients it is sufficient and perhaps more desirable to differentiate lower tract from upper tract infections. The latter term refers to kidney involvement with its potentially serious implications for the general health and prognosis of the patient. Lower tract infections are limited to urethra, bladder and their appendages with emphasis on the *local* nature of the involvement, which usually does not affect the patient's general health, even when marked chronicity is established. The term pyelitis probably should not be employed at all, for isolated involvement of the kidney pelvis is most doubtful. When symptoms referable to the kidney are present, one can generally assume that the parenchyma participates in the inflammatory reaction.

The diagnosis of upper tract or lower tract infection influences the physician's attitude toward the plan of therapy, its urgency and intensity. Nevertheless it is most pertinent to remember that the urinary tract with all its structures and tissues presents, physiologically as well as anatomically, a continuous unit which always must be considered as a whole rather than the sum of its parts.

Similarly it is somewhat artificial to separate acute from chronic infections of the urinary tract. These terms are useful for describing the nature of symptoms and signs but have limited meaning in pathogenesis and treatment. An acute infection may imperceptibly develop into a chronic lesion, just as a chronic infection may manifest itself with acute exacerbations resembling an initial episode. The histologic appearance may be sufficiently succinct to warrant the terms "acute" or "chronic," but usually mixtures of both elements are encountered.

The infections of the urinary tract dealt with in this review are "primary," i.e., not a sequel to active infection elsewhere in the body and caused almost exclusively by micro-organisms which form part of the normal flora of the human body, particularly in the intestinal tract. Specific systemic infections, e.g., tuberculosis or mycoses, in which the urinary tract is involved secondarily to other organs will not be considered in detail. Likewise, specific forms of urethritis, e.g., gonorrhea and abacterial urethritis, will be mentioned only in passing. The management of isolated urethritis, prostatitis and cystitis has long been the province of the urologist.

## PATHOGENESIS

A. Sources of bacteria and pathways of infection.—The normally functioning healthy urinary tract contains no bacteria except for a small indigenous urethral flora. Micro-organisms can reach the urinary tract by four distinct routes: (1) direct extension of an infectious process; (2) through the blood stream; (3) through lymphatics; (4) through external contamination of urinary orifices, with subsequent ascending propagation of micro-organisms within the urinary duct system.

1. *Direct extension* of an infection into the urinary tract might be from a psoas abscess, diverticulitis of the sigmoid, a perinephric abscess, or a pelvic inflammatory process. This is relatively uncommon; it usually involves pathogenic, invasive micro-organisms and thus does not fall into the category of "primary" urinary tract infection being considered here.

2. *The hematogenous route.*—The blood stream serves as vehicle for invasive, pathogenic micro-organisms which cause infection in some part of the body, e.g., tubercle bacilli from the lungs, hemolytic staphylococci from a furuncle. These again do not cause "primary" urinary tract infection but give rise to metastatic abscesses or granulomas in the renal cortex. The blood stream, however, also carries occasional bacteria from the normal flora of the respiratory and intestinal tracts. These asymptomatic, intermittent bacteremias may result in the lodging of such organisms in glomerular tufts, perhaps initiating "primary" urinary tract infection. This is unproved and must be rare, if it does occur.

3. *The lymphatics* (paraurethral, paravesical, paraureteral, and connections with the mesenteric system) probably are the most important routes of access of bacteria to the urinary tract. By virtue of lymphatic connections between the urinary and intestinal tracts the intestinal flora serves as the main source of organisms.

4. *So-called "ascending" or uriniferous infection* presumably results from contamination of the urethral meatus with microorganisms (chiefly fecal flora) and subsequent migration of such organisms against the urinary stream. This is a favored explanation for the greater frequency of urinary tract infection in small girls than in boys. With motile gram-negative bacilli, or in the presence of marked urinary stasis, such a mechanism is both plausible and experimentally established. In the normally functioning urinary tract, there are formidable obstacles to such "ascending" infection, and it is likely that most bacteria are not carried in the urinary tubular system "moving upstream" but rather move proximally in the lymphatic network.

Of these mechanisms, the first two are of much less importance in the common "primary" urinary tract infection than the last two. It is likely that bacteria gain access to the urinary tract by more than one route. In most clinical cases it is not possible to arrive at a definitive conclusion concerning the bacterial pathway.

B. Urinary stasis and obstruction to free flow.—In the presence of normal, unobstructed urinary flow, "primary" urinary tract infection is far less common than in the presence of stasis. Free flow may be impaired by mechanical obstructions or by functional disturbances. Among mechanical obstructions, the following categories are important.

1. *Congenital anomalies.*—Stenosis of the urethral meatus; constriction of the bladder neck; membranous valves at the ureterovesical junction; anomalous blood vessels crossing the ureter; ureteral stenosis or kinks; strictures of the ureteropelvic junction.

2. *Acquired obstructions within the urinary tract.*—Urethral stenosis due to fibrosis following urethritis (rare); calculi in bladder or kidney; enlargement of prostate (due to prostatitis [rare], benign prostatic hypertrophy, prostatic neoplasms); fi-

brotic stenosis in the tract following injury or instrumentation; fibrotic stenosis or deformity of calix following past infection, tumor anywhere in the tract.

3. *Acquired obstruction due to extrinsic pressure on the urinary tract.*—Any pressure on the structures of the urinary tract may result in significant stasis or obstruction. Such pressures might be due to injury (edema, hemorrhage), extrinsic fibrosis following surgery or irradiation, masses (inflammatory or neoplastic) in the abdomen or pelvis and, most commonly, pregnancy. During the second and third trimesters of pregnancy the gravid uterus provides sufficient pressure on the ureters to result in significant urinary stasis, in addition to the relative atony mentioned below.

4. *Functional disturbances of flow.*—Urinary stasis may be due not only to mechanical obstruction but to an impairment of the normal peristalsis and propulsive forces. These may be associated with damage to nerve supply of the musculature of the urinary tract, e.g., spinal cord lesions (cord bladder), traumatic or operative injury to extrinsic or intrinsic innervation, invasion by neoplasm and other influences resulting in "adynamic stasis." During pregnancy, atony of the ureter and bladder may have a hormonal basis. There are, in addition, minor functional derangements of urinary flow which cannot be readily demonstrated by available techniques but produce enough stasis to favor the development of infection. Prolonged recumbency, e.g., protracted bed rest, is such a contributory factor. A marked reduction in urine volume due to dehydration, or inadequate fluid intake, may similarly predispose to infection.

When the degree of mechanical or functional obstruction and its duration are sufficient, dilatation above the point of obstruction eventually develops. If the obstruction is in the bladder or below, ureteral and renal dilatation tends to be bilateral; if the obstruction is at the ureterovesical junction or above, it will be unilateral.

C. Other predisposing features.—Any form of trauma, particularly following instrumentation, predisposes to urinary tract infection. In addition, urologic instrumentation often introduces a large bacterial inoculum into the bladder or even the ureter. Sexual intercourse often precipitates an acute attack of

urinary tract infection (e.g., "honeymoon pyelitis"), but the basis of the physiologic disturbance is not understood. It may be associated with some changes in lymphatic flow that accompany sexual stimulation and intercourse. Similar mechanisms have been postulated for the urinary tract infections precipitated by marked constipation or diarrhea. Systemic diseases which predispose to infection anywhere in the body do so likewise in the urinary tract. Diabetes, for instance, predisposes to urinary tract infection and, in addition, to a particularly severe form of pyelonephritis, papillary necrosis. Stones in the bladder or kidney "lower resistance" to infection (in addition to producing obstruction) perhaps by direct trauma to mucous membranes.

D. COMMON INFECTING MICRO-ORGANISMS. — The following micro-organisms are most frequently cultured in urinary tract infections: coliform bacilli (especially Escherichia coli, Aerobacter aerogenes), paracolon bacilli, streptococci (especially Str. faecalis), staphylococci, Proteus and Pseudomonas. Salmonella, Bacteroides and gram-positive bacilli are occasionally encountered. Not infrequently, two or three different bacterial species are present simultaneously.

## PATHOLOGY

From the ureter to the urethra the changes that occur with urinary tract infection are those of acute pyogenic inflammation, sometimes with a marked hemorrhagic element, which gradually are replaced by chronic inflammatory changes with predominant mononuclear infiltration and which eventually resolve completely or lead to some degree of fibrosis. The fibrosis of the interstitial tissue of bladder and prostate is important because it impairs normal function and serves as a reservoir of infection. The most important pathologic changes in urinary tract infection occur in the kidney, and these will be described in some detail.

If bacteria reach the kidney through the blood stream, the initial lesions occur in the glomerular tuft. This is the case most frequently with staphylococci and streptococci but is a sequence to many other bacteremic processes. A small infected embolus lodges in a capillary of the gomerular tuft or a thrombus forms there. An acute inflammatory reaction follows in the immediate

vicinity and a small abscess forms. The inflammation extends both to the proximal tubule and to the interstitial tissue and soon involves the lymphatics of the corticomedullary region. From there the inflammatory process may reach the calices through tubules and spread down the urinary passages.

The development of lesions following "ascending" and lymphogenous infection in man is not as clearly understood. However, from studies in experimental animals it appears that bacteria which reach the kidney pelvis produce an initial lesion at the calyceal angle, which forms a recess with relative urinary stasis (1). After penetrating the epithelium, bacteria spread through the lymphatics of the arcuate vessels to the corticomedullary junction and from there to the interstitial tissue, blood vessels and tubules, or to cortex and capsule, eliciting inflammatory changes in all of these structures. Multiple inflammatory foci are scattered throughout the interstitial tissue, particularly adjacent to blood vessels. They begin as accumulations of polymorphs and monocytes and may progress to frank abscess formation. Some blood vessels are thrombosed. It is probable that lymphogenous bacteria result in a similar pattern of changes.

Once significant numbers of bacteria have reached the kidney and established themselves, the progression of the pathologic process is independent of the initial route of infection. Isolated abscesses may remain limited to a small area of the interstitial tissue and slowly resolve or undergo fibrosis. They may extend into tubules and the inflammation may spread along them to reach the papilla and calix. Although most acute or subacute lesions can heal without leaving any signs, chronic inflammation causes pronounced changes. Chronic infection of the pelvis results in extensive peripelvic fibrosis with distortion of the shape of calices. Tubules are dilated with flattened epithelium and filled with colloid-like casts. The walls of arterioles are thickened. Most important in chronic pyelonephritis are the widespread interstitial lesions, with destruction of the parenchyma and its replacement by granulation and scar tissue. If this occurs in limited areas the depressed, fibrotic scars of old pyelonephritis replace the cortex in angular shapes. If the fibrosis is widespread the small contracted, nonfunctioning kidney with almost total destruction of the parenchyma is the end result. Often fibrous

scars and acute inflammatory lesions testify to the recurrent activity of the infection. Late in the chronic process there may be localized or diffuse thickening of arterioles; the resulting ischemia may be important in the genesis of hypertension (resembling "Goldblatt kidney").

The interstitial lesion of the kidney parenchyma is important, not only because it results in increasing impairment of function but also because, due to its avascular, fibrous nature, it serves as a continuing reservoir of infection which presents unusual problems to chemotherapy.

## SIGNS AND SYMPTOMS

The clinical manifestations of active urinary tract infection are those of local or systemic infection, inflammation of mucous membrane and smooth muscle spasm. The late renal insufficiency resulting from chronic pyelonephritis gives rise to the same events as renal insufficiency from other causes.

In general, infection of the lower tract is associated with pain in the urethra and bladder, dysuria, urgency, frequency, nocturia, occasionally hematuria; rarely fever or flank pain. Although fever is very uncommon in acute cystitis, it is a frequent manifestation of acute prostatitis.

Acute infection of the upper tract is associated with pain in flank, back and abdomen, often radiating to the groin, and costovertebral angle tenderness. There are spiking fever and chills. Lower tract symptoms are usually also present. Anorexia, nausea and vomiting may suggest a gastrointestinal disorder or cholecystitis. Urinary findings are presented in the next section.

In chronic pyelonephritis, symptoms of infection are often lacking. With renal failure there may be hypertension, edema, anemia, symptoms of uremia, with or without symptoms of active infection.

## NATURAL HISTORY OF URINARY TRACT INFECTION

It had long been suspected that some connection existed between the acute, brief episodes of manifest urinary tract infection and the ultimate development of renal failure. The masterful ob-

servations of Longcope and Winkenwerder (2) and Weiss and Parker (3) suggested that often a process of persistent inflammation smoldering below the level of manifest symptoms connected the episodes of clinically evident activity of urinary tract infection and resulted in progressive scarring and fibrosis in the urinary tract, particularly the kidney. Such a progressive course, however, is the exception rather than the rule, as indicated by the finding of the scars of healed pyelonephritis in nearly 14% of 1,000 consecutive autopsies at the Boston City Hospital (4). Thus pyelonephritis often heals spontaneously. Conversely, it may sometimes be a very malignant disease with rapid progression to renal failure, as in papillary necrosis which occurs in up to 20% of diabetic patients with urinary tract infection. How the pleomorphic nature of urinary tract infection may fit into a basic pattern may be illustrated with the hypothetical life history of a female patient with urinary tract infection (Fig. 1).

As a young child this patient had an acute febrile illness diagnosed by the pediatrician as acute pyelonephritis, perhaps associated with some minor anatomic anomaly of the urinary tract. Even this initial episode might have been mild and not associated with clearcut symptoms referable to the urinary tract. Subsequently the process was quiescent, or only minor flare-ups occurred during adolescence, perhaps suggestive of "urethritis" or undiagnosed back pain. Shortly after marriage, at 19, the patient had an attack of "honeymoon pyelitis" which quickly subsided with mandelic acid treatment. During pregnancy a year later, "pyelitis" developed in the seventh month, with considerable discomfort, fever, back pain, dysuria and frequency. There was, fortunately, no toxemia, and a normal delivery was followed by a period of normal health. A few years later she consulted a urologist for the first time because of recurrent attacks of lumbar aching, dysuria and urinary frequency. Urinary tract infection was diagnosed, organisms were demonstrated in the urine, but her kidney function was good. In spite of various forms of treatment the complaints persisted or recurred, and occasionally there was a little fever with attacks. The patient also frequently noticed turbidity and a strong odor of her urine. Gradually fatigue developed and the patient was referred to an internist because of anemia. This physician found moderate hypertension,

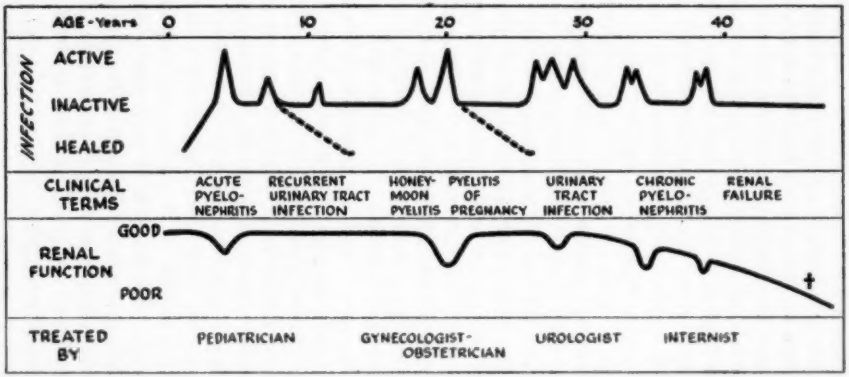



FIG. 1.—Life chart of a female patient with urinary tract infection. (Figs. 1 and 2 from California Med. 79:99-102, August, 1953.)

proteinuria, marked nitrogen retention—all signs of progressive renal failure. From then on the course rapidly led to uremia and cardiac failure—or perhaps it progressed slowly over many years.

At any time during childhood or adult life, prior to the beginning of renal insufficiency, the infection might heal completely. In addition, there are many patients who have recurrent evidence of pyelonephritis but, even over a period of many years, show no evidence of impaired renal function. It is generally not possible to predict, in an individual without obstruction, into which part of this very wide spectrum of disease he might fit. It is furthermore evident that many persons (particularly females) will have no apparent symptoms of urinary tract infection whatever until manifestations of renal insufficiency develop. In a series of 3,000 unselected autopsies, Ophuls found "active septic infection" of the urinary tract in 4.8% (5). In an unselected group of 100 women attending a medical clinic, the incidence of urinary tract infection was 19% (6). Although only six had symptoms, some of these individuals are likely to have renal failure in later life.

Looking at urinary tract infection as a long-term problem and not as a series of brief, unconnected episodes, it becomes clear that the important site of infection is not the urine, or the duct system from glomerulus to bladder, but the interstitial tissue. Regardless of the route by which bacteria reach the kidney, it is the chronic inflammation within the parenchyma which leads to destruction of nephrons and fibrosis and determines chronicity, and ultimate outcome. The management of urinary tract infections may profitably be considered from this point of view.

Another difficulty, stressed by Birchall (7), is the discontinuity in therapeutic management. Each episode of manifest urinary tract infection is being treated as an isolated event by a different physician (pediatrician, gynecologist, obstetrician, urologist, internist). For optimal management of the patient a different, long-term approach is desirable.

## DIAGNOSTIC METHODS

To permit proper management of urinary tract infections, diagnostic procedures must establish: *(a)* the status of kidney

function; *(b)* the presence of anatomic obstructive lesions and other predisposing factors; *(c)* the specific etiology of the infection, with isolation of the infecting micro-organism.

History and physical examination often suggest the diagnosis of urinary tract infection. Sometimes the illness masquerades as a gastrointestinal disorder or a fever of undetermined etiology, and often no symptoms at all are present. Routine laboratory examination may be helpful. The blood commonly shows elevated leukocyte counts with a shift to the left in acute pyelonephritis. Anemia may be the earliest sign of incipient uremia. In chronic pyelonephritis the sedimentation rate is often elevated.

Routine urinalysis can generally establish the diagnosis beyond doubt. Urine is best obtained from a continuous stream in three successive clean glasses. The first glass reflects events in the mucous membrane of the urethra, for the first part of the stream carries with it cells, mucus and organisms of the urethra. The second glass commonly mirrors events higher up in the urinary tract (bladder and kidney) and is the most useful part of the stream for bacteriologic examination of possible renal infection. The end of the stream (third glass) often contains cells and bacteria from prostate and posterior urethra.

In the presence of acute infection, microscopic examination of fresh urine usually reveals many pus cells, occasional red cells and some bacteria, but rarely casts. The urine may be entirely normal when the inflammatory lesion does not involve, or communicate with, the tubular system (e.g., perinephric infection, cortical abscess, interstitial focus) or if there is a unilateral block in the urinary passages, most commonly the ureter.

In subacute or chronic urinary tract infection one often also encounters both pus cells and bacteria. However, either of these may be present without the other. Furthermore, the result of any single examination of urine may be altogether negative in the presence of chronic interstitial lesions in the kidney parenchyma. Only repeated examinations can detect the intermittent showers of bacteria and occasional discharge of inflammatory cells.

Protein is rarely found when the infection is limited to the lower tract unless there is hemorrhagic cystitis, ulcerated lesions or other sources of blood or exudate. Proteinuria is transitory in most cases of active pyelonephritis but only irregularly present

in early chronic pyelonephritis. There is usually proteinuria in the dilute urine of marked renal insufficiency of chronic pyelonephritis.

Blood and urine examinations are indicated in every case of suspected urinary tract infection. The examinations listed below must be applied with judgment in the individual case. The timing of proposed diagnostic and therapeutic management is outlined at the end of this review.

TESTS OF RENAL FUNCTION.—Renal function tends to be good in pyelonephritis until far-reaching destruction of the parenchyma has taken place. However, the excretory function may be temporarily depressed during the acute intense inflammation of active pyelonephritis. It is useful to know the efficiency of renal excretion so that excretory urograms may be properly planned and not uselessly imposed on the patient. If the result of the simple phenolsulfonphthalein excretion test is within normal limits, it may be assumed that the excretion of Diodrast (or other radiopaque material) will be adequate. It is equally simple and useful to establish some measure of retention of nitrogenous waste products (e.g., blood urea, nonprotein nitrogen or creatinine). For more complete information on excretory function of the kidney, one of the several clearance tests (e.g., creatinine clearance) may be used in chronic urinary tract infections.

PROCEDURES TO DETERMINE PRESENCE OF OBSTRUCTION OR DEFORMITY.—Plain x-ray films of the urinary tract may detect calculi in any part of the tract and permit an estimate of kidney size. Only a portion of calculi, the markedly radiopaque ones, can be clearly seen, but they comprise the majority. Intravenous, excretory urography is the next step, provided the kidneys are capable of concentrating the dye sufficiently for good contrast. It may reveal obstruction, dilatation above obstruction, distortion of the normal pattern of shadows or poor unilateral excretion of dye, indicative of impaired function or stasis. Deformities of calices or ureters seen in urograms are an expression of scarring, fibrosis and consequent distortion. Acute urinary tract infections, even with widespread inflammatory changes in the kidneys, are not likely to be noticed on urograms.

Cystoscopy provides direct information on the patency of the lower urinary tract and the appearance of its mucous membranes.

The latter may indirectly reflect the involvement of the upper tract; e.g., inflammatory changes around the ureteral orifices suggest "seeding" of micro-organisms from above. Catheterization of the ureteral orifices during cystoscopy provides opportunity for the collection of separate urine specimens from each side for bacteriologic examination and for differential phenolsulfonphthalein tests. Determination of possible residual urine in the bladder is an important part of cystoscopic procedure.

Retrograde urograms are the "last resort" to determine anatomic anomalies. They must not be performed in the presence of acute infection, unless mechanical relief of ureteral obstruction is necessary. They must be carefully planned so that all possible information can be obtained simultaneously from instrumentation, including specimens from both ureters for differential urine cultures and differential phenolsulfonphthalein excretion tests. In the presence of significant renal insufficiency the advisability of the procedure must be weighed against the risk, and special caution must be exercised in performing retrograde studies. Care must be used to avoid excessive pressure in instilling the dye, because sudden impairment of renal function with marked nitrogen retention may result, in addition to severe pain, nausea and vomiting. The instrumentation necessary for retrograde urograms may induce bacteremia. This is of particular concern in patients with valvular heart lesions in whom bacterial endocarditis may ensue.

BACTERIOLOGIC EXAMINATION OF URINE.—Optimal management of urinary tract infection depends to a large extent on the identification of the specific infecting organism and determination of its sensitivity to antimicrobial drugs. Proper and complete bacteriologic examination includes the following steps (but not all of these procedures are indicated in every patient).

1. Proper collection of urine specimen. Urine should be collected before the administration of antimicrobial agents, in sterile containers, preferably cotton-plugged test tubes. Containers must not contain disinfectant or other chemicals. In females, specimens to be used for culture must usually be obtained by catheterization. In males, thorough cleansing of the urethral meatus (e.g., with mercury bichloride 1:1,000), discarding of the initial part of the urinary stream and collection of the "mid-

portion" (equivalent of the second glass specimen) give satisfactory specimens.

2. Examination of the specimen. This must be done promptly. Unless the specimen is delivered to the laboratory and examined within one hour after collection, bacteria will either multiply or die. Depending on pH, specific gravity, cells and organic materials present, the total number of micro-organisms as well as their relative proportions may change when the specimen is left standing at room temperature.

3. Microscopic examination. *(a) Unstained wet preparation:* A drop of fresh urine is placed on a glass slide, covered with a cover slip and examined under the high-dry objective, with low light intensity. This is particularly useful with turbid urine, for it quickly shows whether the turbidity is due to precipitate, crystals, cells or bacteria. Furthermore, a rough estimate of the prevalence of cells and bacteria can be made, and motile rods can sometimes be quickly differentiated from cocci. A similar examination can be carried out with clear urine centrifuged at about 2,000 rpm for several minutes. The sediment may contain a moderate concentration of the number of cells and bacteria, as compared to the uncentrifuged specimen. *(b) Stained smear:* A loopful of fresh urine, or of the centrifuged sediment, is smeared onto a glass slide, air-dried, briefly fixed in the flame and stained. Simple methylene blue stains permit differentiation of rods from cocci and a rough estimate of numbers per milliliter of urine. In stained smears, bacteria are readily seen without searching only when their number exceeds 10,000–100,000 per ml of urine sediment. For further differentiation, gram stains are desirable.

4. Qualitative culture. To determine the types of bacteria present, fresh urine, or centrifuged sediment, is streaked onto blood-agar, and eosin-methylene blue (or Endo's or McConkey's) agar plates, and inoculated into thioglycollate medium and meat-infusion broth. After incubation this permits the isolation and recognition of aerobic as well as anaerobic organisms and the rapid colonial identification of the common varieties (staphylococci, streptococci, coliform bacteria, Proteus, Pseudomonas). Initial disk-type sensitivity tests may be performed directly on these initial qualitative streak plates (see paragraph 7).

5. Quantitative culture. Qualitative cultures only determine the kind of bacteria but give no indication of their number. Since the urine of normal persons may contain up to 100–500 organisms per ml, largely from the urethral flora or from unavoidable minimal contamination in the course of collection, quantitative culture is essential. Larger numbers of bacteria, in excess of 500–1,000 per ml of urine, even in the absence of pus cells, denote urinary tract infection. When urine is obtained directly from ureter or kidney pelvis, any number of bacteria is significant. However, when a catheter traverses an infected bladder it may carry some bacteria into the ureter. Therefore the end of ureteral catheters should be plugged.

Quantitative cultures are performed by spreading 0.1 ml of clear undiluted urine and 0.1 ml of a 1:100 dilution on suitable mediums. If the urine is turbid, additional plates are made with 1:10,000 and even with 1:1,000,000 dilutions. Agar pour plates are equally satisfactory but do not permit the easy differentiation of colonial forms. The plates are incubated and then the colonies counted.

6. Special bacteriologic studies. In some patients there is good clinical and laboratory evidence of infection, but no ordinary bacteria can be recovered from the urine. If localized or walled-off infection can be excluded (e.g., perinephric or cortical abscess, blocked ureter), laboratory studies for other types of micro-organisms must be carried out. Most important is the search for anaerobic cocci and bacilli. The suspicion of tuberculosis requires acid-fast staining of the centrifuged sediment, special culture methods and guinea pig inoculation of concentrated urine. When pleuropneumonia-like organisms, or fungi, are suspected of playing an etiologic role, special culture methods have to be employed.

7. Antibiotic sensitivity tests on bacteria isolated from the urinary tract. The principal reason for isolating the etiologic micro-organisms is not the academic one of specific diagnosis for its own sake but the urgent need to determine the antimicrobial drug most likely to be effective against the particular micro-organism. With the extensive use and misuse of antibiotics, many patients now harbor bacteria which are resistant to one or several drugs.

The rapid, qualitative *"disk" method* of antibiotic sensitivity testing, in spite of many inadequacies, often gives valuable leads as to which drugs are likely to inhibit the infecting micro-organisms and, of equal value, which drugs should not be used because the organisms appear to be completely resistant to them. While this is only a partial answer, it can be obtained rapidly and cheaply. If a proper urine specimen is submitted to the laboratory in the afternoon, antibiotic-saturated paper disks are placed on the initial qualitative culture plate, and the inhibition zones observed around the disks the next morning will inform the physician of the drugs "likely to be effective." With good collaboration between physician and laboratory these results can give valuable guidance to therapy. A small proportion of results will inevitably give misleading information, because the simple in vitro test does not parallel the complexities encountered in vivo (see under Therapeutic Management). In most instances the determination of sulfonamide sensitivity in the routine laboratory is not very satisfactory or reliable.

The disk test is a fairly useful qualitative guide, but it gives no quantitative information and does not permit the distinction between drugs which merely inhibit and those which kill the infecting organism in a given concentration. To obtain such information it is necessary to resort to more elaborate *"tube-dilution" tests.* Graded concentrations of antibiotic in broth tubes are inoculated with known numbers of the infectious micro-organism and, after incubation, the drug concentration is determined which is capable of inhibiting growth or of killing all exposed micro-organisms (i.e., the subculture of the mixture is sterile). These tests are more expensive and time-consuming but occasionally give valuable information for the guidance of chemotherapy (discussed later).

## DIFFERENTIAL DIAGNOSIS

In the presence of active signs and symptoms, infection of either the upper or the lower urinary tract is not difficult to diagnose. Confusion might arise with any other abdominal infection, with gastrointestinal disorders, retroperitoneal inflammation or tumor, subdiaphragmatic inflammation and even basal

pleural lesions. Acute perinephric inflammation resembles acute pyelonephritis in all respects, except for the absence of pus cells and bacteria in the urine, in the presence of demonstrably patent ureters. Perinephric abscess obliterates the x-ray shadows of kidney and psoas, often displaces kidney and ureter and elevates the diaphragm. It may also result in scoliosis with concavity of the spine to the affected side from psoas spasm. Abscesses of the renal cortex produce an acute, septic picture but cannot be clearly differentiated from other forms of acute pyelonephritis unless there has been sufficient destruction to produce anomalies in the urogram. Cholecystitis with anorexia, vomiting, pain and fever may present a difficult differential point.

Often, however, symptoms and signs pointing to the urinary tract are entirely lacking, and the patient presents himself with the complaints of lassitude, loss of weight and low grade fever. In such circumstances, it is important to consider urinary tract infection as one of the causes of fever of unknown origin, which must be investigated.

Clinical manifestations of lower urinary tract infection, particularly cystitis and prostatitis, may be the only sign of a process which also involves the upper tract. Particularly in interstitial cystitis and chronic prostatitis, one may sometimes find the manifest residual foci of chronic silent pyelonephritis.

## THERAPEUTIC MANAGEMENT

To cover all aspects of the disease, the management of urinary tract infection properly falls into three categories: *(a)* correction of structural abnormalities of the tract; *(b)* treatment and, if possible, eradication of the infection; *(c)* palliative therapy of renal failure and disturbances associated with it.

The first of these is in the province of the urologist. Adequate drainage is essential for the successful treatment of all suppurative inflammation. If drainage of urinary tract infection is inadequate, recurrences and chronicity are inevitable. Therefore, if obstruction is suspected a competent urologist must be consulted. Investigation and correction are carried out by specialized methods, employing instrumentation and surgery, and will not be reviewed here. The third, the treatment of renal insufficiency,

nitrogen retention, uremia, hypertension, cardiac insufficiency and other associated conditions, requires careful attention to detailed management of fluids, electrolytes, diet and other such factors. Expert guidance along these lines will often keep a patient alive and in good condition to receive antibiotic therapy. The details of the treatment of renal insufficiency are a specialized field in itself.

The discussion here is principally concerned with the second of the three categories of management mentioned—the treatment of the infectious process. By optimal therapy the infection may be eradicated and the organic damage to the kidney may be prevented.

A planned attack on the infectious process includes a specific etiologic diagnosis, selection of appropriate antimicrobial agents, administration of drugs in adequate doses for a sufficient time, and prolonged follow-up to establish cure with certainty. The first of these, the determination of etiologic agents by bacteriologic methods, has already been considered. The principles and limitations of chemotherapy and the role of certain specific drugs will be discussed here.

## Principles of Chemotherapy in Urinary Tract Infection

The methods have been outlined which are employed to determine the "drug most likely to succeed" by laboratory tests. Whereas any in vitro test matches a drug against an organism, in vivo the situation is complicated by the interaction of both drug and organism with the host as well as with each other. This can be pictured schematically as a triangular relationship where each interaction influences the other two. For the sake of simplicity, however, it is preferable to take up each of the relationships separately and see how they would influence ideal therapeutic management.

Host-microbe relationship.—In the early stages of bacterial invasion and host response, the micro-organisms are in

relatively vascular tissue, accessible to drugs and to phagocytic cells. The longer the infection in interstitial tissue persists, the more dense avascular fibrous tissue is deposited, as a formidable obstacle to drugs and phagocytic cells, and the more difficult becomes the eradication of the infection. It has already been said that in pyelonephritis there is primarily infection in the interstitial tissue of the kidney. The involvement of the urinary passages is often secondary. The condition of the urine may be only a manifestation of the neighborhood involvement of renal tissue and inflammation of the lower tract. On the other hand, the urine may be sterile and without pus cells even though there is active and progressive inflammation in the renal parenchyma. Logically, treatment should not be limited to sterilization of the urine, which can be readily accomplished, but must be directed to the eradication of the infection in tissues, particularly in the renal parenchyma.

DRUG-MICROBE RELATIONSHIP.—Under the conditions just described, a chemotherapeutic drug, in order to influence a urinary tract infection significantly, will have to act within the interstitial tissues of the kidney. Consequently "urinary antiseptics," i.e., drugs which have antimicrobial properties only when in acid urine, like the mandelic acid salts, would have little effect. These substances might temporarily sterilize the urine but would be quite unable to influence the infection in the parenchyma. They provide symptomatic relief but do not attack the source of trouble. The matter of "urinary dose," based on similar reasoning, is discussed later.

In view of the nature of the pathologic lesions already described, it is evident that spontaneous complete healing of acute or subacute pyelonephritis takes place only in a certain proportion of cases. In the remaining cases it may be assumed that the normal anti-infectious defenses of the body are incapable of eradicating the process, which then progresses to chronicity and irreversible damage. It therefore appears desirable to use drugs which do not rely greatly on the contribution of the host but are capable of killing the micro-organisms outright on contact, in concentrations which can be attained in tissue. Thus drugs or drug combinations which are bactericidal at the usual dosage are probably better than drugs that are principally bacteriostatic.

Needless to say, since eradication, not merely suppression, of the infection is the aim of treatment, drug administration must be continued for a sufficient time to permit all micro-organisms to be killed.

HOST-DRUG RELATIONSHIP.—In view of the nature of the lesions in interstitial tissue, one of the features limiting the effectiveness of antimicrobial drugs is their ability to penetrate in significant concentration through relatively avascular tissue to reach the micro-organisms. Since there must be a considerable diffusion gradient between the concentration of the drug in the blood stream and its level in the inflammatory lesion, small molecular drugs with good diffusing properties are desirable.

Most antimicrobial drugs are excreted largely through the kidneys and concentrated in the proximal convoluted tubules. Consequently, the drug concentration in the urine tends to be much higher than that in body fluids or tissues. For this reason, it has become customary to use small, so-called "urinary doses" of antimicrobial drugs which result in urinary concentrations sufficient to inhibit most infecting micro-organisms. Thus, 0.5 gm of a sulfonamide taken four times daily results in a concentration of about 50 mg of the drug per 100 ml of urine but would obviously not be an adequate amount to produce satisfactory systemic tissue levels of the drug. If such "urinary doses" of antimicrobial drug are taken for a few days the urine is usually "sterilized" promptly, and symptoms, particularly of lower urinary tract involvement, subside. Cultures taken during therapy and immediately thereafter are negative. This may lead to the belief, often unwarranted, that the patient is "cured." Actually, the infection often has only been suppressed, and it relapses soon after treatment, when micro-organisms emerge from the interstitial lesion barely touched by "urinary doses."

From these considerations some conclusions pertaining to the ideal choice and use of drugs can be drawn. The urinary tract infection must be diagnosed *early* before the interstitial tissue lesion has fibrosed. The etiologic organism must be isolated and the drug selected which *kills it rapidly in vitro.* This drug must be administered in *full systemic doses* for *two to three weeks.* Cultures must be negative during and after treatment, and they must remain so during the follow-up period of two months. It

will become apparent that such an ideal sequence of events is not common.

With the foregoing principles in mind, it is now possible to scrutinize the available chemotherapeutic agents for their probable usefulness in urinary tract infections.

A. SULFONAMIDES.—This group of drugs has the advantages of antimicrobial effectiveness against a wide variety of organisms, including those commonly encountered in urinary tract infections; cheapness and availability; relatively low toxicity, and good distribution in tissues. A disadvantage is their definite bacteriostatic character, even in large doses. Although a dose of 0.5 gm four times daily gives urinary levels of 50–130 mg%, it is preferable to use larger doses (4–8 gm daily) in order to achieve adequate tissue levels. The fluid intake must be kept above 2,500 ml daily, and the urine should preferably be kept alkaline, if necessary by the administration of sodium bicarbonate. In urinary tract infections with recurrent activity, when repeated attempts at eradicating the infection have failed, suppressive doses of 0.5 gm of a sulfonamide daily are sometimes employed for long periods.

The sulfonamides, widely distributed in tissues (e.g., sulfadiazine, sulfamerazine, sulfathiazole), are perhaps preferable to those that produce particularly high urine levels at the cost of tissue levels (e.g., sulfisoxazole = Gantrisin), in spite of high solubility of the latter. Sulfonamide mixtures, (three, four or more) have the advantage of greater solubility in urine but are not more effective, and possibly less, than single drugs.

B. TETRACYCLINES (tetracycline = Achromycin, Tetracyn; chlortetracycline = Aureomycin; oxytetracycline = Terramycin). —These drugs share the wide antibacterial spectrum of the sulfonamides, although Proteus and Pseudomonas are frequently resistant and resistant coliform bacteria are encountered with increasing frequency. The three agents give almost complete cross-resistance: if a microbial strain is resistant to one of the three drugs, it is usually resistant to all. The tetracyclines are principally bacteriostatic but in very high concentrations are also bactericidal. Tetracycline is said to be better tolerated than the other two, but the incidence of gastrointestinal side effects is probably similar with all three drugs. For urinary tract infections

the dose should be 0.5 gm two to four times daily, by mouth.

C. CHLORAMPHENICOL (Chloromycetin).—This drug resembles the tetracyclines in most properties, but it gives only slight cross-resistance with them. Thus tetracycline-resistant micro-organisms often remain chloramphenicol-sensitive. The toxicity of this drug for the hemopoietic system has been much exaggerated. Nevertheless it should be used only when clearly indicated. This maxim, however, applies equally to all other antimicrobial agents. The dose should be 0.5 gm two to four times daily, by mouth.

D. PENICILLIN.—This ideal chemotherapeutic agent has, unfortunately, very limited application in urinary tract infections, because the majority of infecting micro-organisms (gram-negative bacteria) are not affected by it. It may occasionally be used against sensitive staphylococcic infections and, in combinations with other drugs, against fecal streptococci. Many other streptococci are readily killed by penicillin. The dose depends entirely on the sensitivity of the organism. Up to 100,000,000 units daily have been administered to patients without toxic effects. Unfortunately, hypersensitivity reactions are observed in 5–10% of patients.

E. STREPTOMYCIN AND DIHYDROSTREPTOMYCIN.—The antimicrobial properties of these two drugs are identical and cross-resistance is complete. All bacterial strains form mutants which are resistant to high concentrations of streptomycin. These mutants will invariably emerge after three or four days of streptomycin therapy and supplant the previously susceptible flora, unless all infecting bacteria have been killed. Therefore, streptomycin therapy in urinary tract infections is limited to three to four days of 2–4 gm daily, injected intramuscularly. Since streptomycin is quite actively bactericidal, it will occasionally cure acute pyelonephritis. It is futile to continue the drug longer than three to four days unless it is given in combination with other agents (see paragraph J).

F. BACITRACIN.—Since this drug is exclusively active against gram positive bacteria, it can be employed only very rarely. It is sometimes useful against penicillin-resistant staphylococci. It possesses fairly marked nephrotoxicity.

G. ERYTHROMYCIN AND CARBOMYCIN.—These drugs are occa-

sionally useful against penicillin-resistant cocci. Their role in urinary tract infection is not established.

H. NEOMYCIN.—Although this drug has enjoyed little popularity because it sometimes produces sudden deafness and is somewhat nephrotoxic, it can be given in doses of 0.5 gm twice daily, intramuscularly, with reasonable safety. It often affects gram-negative bacilli, particularly Proteus and Aerobacter, which are completely resistant to other agents.

I. POLYMYXIN B AND E.—These two basic polypeptides theoretically might seem almost ideal for eradicating the bacteria of chronic urinary tract infection. They are rapidly bactericidal for gram-negative bacteria, and resistant organisms are rarely encountered. Unfortunately, the large molecular size prevents good diffusion and penetration of the drugs, and their relative toxicity interferes with prolonged use in high doses. They produce unpleasant but harmless neurotoxic effects (paresthesias, dizziness) and are somewhat nephrotoxic, particularly in individuals with impaired renal function. Therefore the dose has to be limited to 2.5 mg/kg/day (maximal daily dose 200 mg), injected intramuscularly, for not more than two weeks. Particularly in acute pyelonephritis due to Pseudomonas aeruginosa and other gram-negative organisms resistant to more common antibiotics, they are the drugs of choice.

J. ANTIBIOTIC COMBINATIONS.—These may be used for one of three reasons. (1) Two different antibiotics may be more effective in combating an infection due to two different micro-organisms than any single drug. (2) One antibiotic may have little activity of its own, but it may delay the emergence of resistant forms to the other antibiotic. (3) The two drugs used simultaneously may have much greater antimicrobial effect than either one alone or than would be expected from simple addition of their effects. This effect is called "synergism"; e.g., penicillin and streptomycin given simultaneously can sometimes eradicate fecal streptococci from a urinary tract infection, although neither alone is notably effective.

K. MANDELIC ACID (CALCIUM, SODIUM OR AMMONIUM SALTS); MANDELAMINE (METHENAMINE MANDELATE); FURADANTIN.—These substances are true "urinary antiseptics." They have no action on tissue lesions at all, having antibacterial effects only in

urine. They do not cure pyelonephritis, but they can keep the bacterial count in the urine down and thus greatly diminish lower tract symptoms in many patients in whom eradication of the upper tract infection is impossible. Thus, they are valuable in treatment but should rarely be the first drug of choice in previously untreated infections. Calcium, sodium or ammonium mandelate, 12 gm daily, is given in divided doses by mouth, with restriction of fluids to 1,200 ml and acidification of the urine with ammonium chloride (1–2 gm four times daily by mouth) necessary to maintain pH below 5.5. With Mandelamine, fluid restriction is unnecessary and a daily dose of 3 gm (3 tablets [0.75 gm] four times daily) acidifies the urine sufficiently. Methenamine as such is little used (it liberates formaldehyde in acid urine) because Mandelamine is better tolerated and more effective.

Furadantin and other nitrofuran derivatives in vitro are effectively bacteriostatic and even bactericidal for a variety of antibiotic-resistant micro-organisms. After oral doses of 5–8 mg/kg/day there are no significant blood levels but concentration in the urine is high. At times the nitrofurans are effective urinary antiseptics especially against gram-negative bacilli which cannot be eradicated. These drugs may induce gastrointestinal side effects and perhaps add to renal damage.

Perhaps pyridium should also be mentioned, although it has no significant antibacterial effect. It acts entirely by "soothing" the bladder mucosa and diminishing smooth muscle irritability. Thus it relieves symptoms somewhat but does not affect the cause.

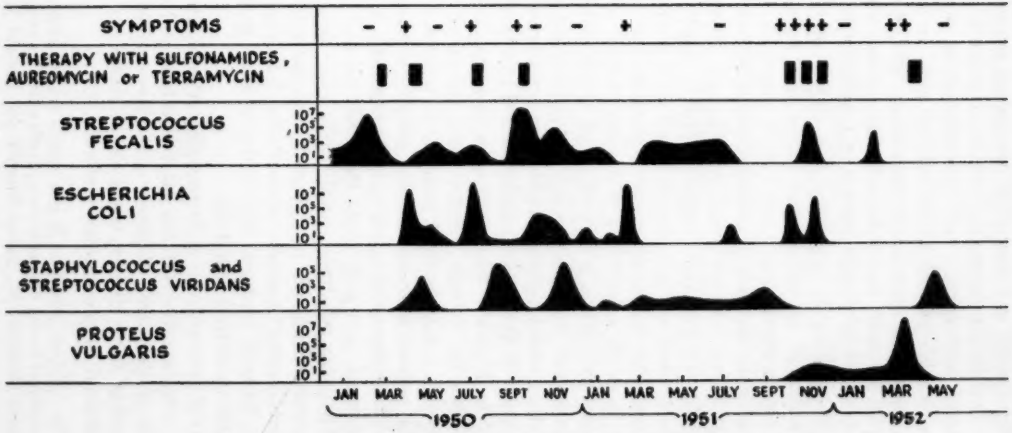
## Practical Management

The preceding sections of this review have presented the basic aspects of pathogenesis, diagnosis and therapy of urinary tract infections. When one is faced with a specific patient, however, the questions invariably arise: When do I take a culture? When, retrograde urograms? What drug do I use first? What next? Universal answers to these questions are obviously impossible. However, a rational sequence can be formulated which offers an acceptable pattern of approach and perhaps a good chance for therapeutic success.

A. The patient is seen during the first clinical attack of urinary tract infection. A three-glass urine specimen is secured in the male, or a catheterized specimen in the female, and microscopic examination of the urine is the only absolutely necessary laboratory examination. Cultures may be made if convenient. The microscopic examination yields information about pus cells and approximate number and kind of bacteria (rods or cocci). If pus and bacteria come from the bladder or kidney (second glass), sulfonamides are started. Depending on the clinical status (fever, pain), bed rest is adjusted, and fluids are forced to 3,500–4,000 ml daily. Sulfonamides are administered for 10 days (4–8 gm daily for adults), and the patient is asked to return for a follow-up examination in three weeks after treatment is stopped, or if symptoms return.

B. The patient is seen during a clinical recurrence of urinary tract infection, or after failure of initial sulfonamide therapy, or because he has bacteria in the urine on follow-up examination. A quantitative urine culture is now important, with antibiotic sensitivity tests to determine appropriate bactericidal agents. The "drug most likely to succeed" is employed for not less than 10–14 days in full dosage. Simultaneously, simple tests for renal function and an excretory urogram are carried out.

C. The patient has had one recurrence of urinary tract infection after sulfonamides and has either failed on antibiotic therapy or has laboratory evidence of persistent infection following a course of "drug of choice"; or the patient is first seen with established chronic pyelonephritis. Complete urologic study, including excretory urography, cystoscopy, retrograde urography, differential phenolsulfonphthalein excretion and differential cultures of urine from both ureters, should be carried out and sensitivity tests performed on organisms isolated from urine obtained from the kidney. If any obstruction or stone is found it must be remedied by a urologist before the next attempt at chemotherapy with the "drug of choice" is made. If infection is shown to be localized in one kidney, the patient must be restudied following additional chemotherapy to decide whether removal of the infected kidney is indicated, particularly if its function is impaired and that of the other side good. Repeated urologic consultation must be advised before such a step is taken.


SYMPTOMS
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THERAPY WITH SULFONAMIDES, AUREOMYCIN or TERRAMYCIN
STREPTOCOCCUS FECALIS
ESCHERICHIA COLI
STAPHYLOCOCCUS and STREPTOCOCCUS VIRIDANS
PROTEUS VULGARIS
JAN MAR MAY JULY SEPT NOV JAN MAR MAY JULY SEPT NOV JAN MAR MAY
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FIG. 2.—Quantitative urine cultures in a case of chronic pyelonephritis.

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